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FAX TRANSMITTAL

DATE: October 23, 2003

TO: Examiner Christopher J. Nichols, Ph.D.

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FROM: Debra A. Gordon, Ph.D., J.D. (Reg. No. 54,128)

RE: FUNCTIONALIZED TGF-BETA FUSION PROTEINS

OUR FILE: 4239-61302

Pat. Appl. No. : 10/017,372

NO. PAGES 7 (including this cover page)

PLEASE ACKNOWLEDGE RECEIPT BY RETURN FACSIMILE? ☐ Yes ☒ No

CONFIRMATION TO FOLLOW? ☐ Yes ☒ No

CONTACT INFO: If you do not receive all pages or if you have problems receiving transmittal, please call us at (503) 226-7391 as soon as possible and ask for Debra A. Gordon, Ph.D., J.D..

MESSAGE: Examiner Nichols:

Attached are draft claims for discussion during our telephone interview with Tanya Harding and me on Monday, October 27 at 1 PM Eastern. Please do not yet enter these claims in the case. We request that you review this draft so we can discuss specific ideas for amending the claims in response to the proposed Examiner's Amendment. As we discussed, the attached claims are redlined against the proposed Examiner's Amendment.

Thank you for your assistance,
Deb

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TMH/DAG:lam:dv 10/23/03 E-149-2000/0-US-02
PATENT

Attorney Reference Number 4239-61302
Application Number 10/017,372

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In re application of: Wolfram and Letterio

Application No. 10/017,372

Filed: October 19, 2001

Confirmation No. 6866

For: FUNCTIONALIZED TGF-BETA
FUSION PROTEINS

Examiner: Christopher J. Nichols, Ph.D.

Art Unit: 1647

Attorney Reference No. 4239-61302

**PROPOSED LISTING OF CLAIMS
(FOR DISCUSSION ONLY)**

This listing of claims shows changes from the claims as set forth in the Proposed Examiner's Amendment:

1. (Currently amended) A functional TGF- β 1 fusion protein, comprising:
a functionalizing peptide tag of no more than about 100 amino acids for detecting, quantifying, or providing a specific additional function to the fusion protein; and
a mature TGF- β 1 comprising residues 279-283 and 296-407 of SEQ ID NO: 37,
or an amino acid sequence that has at least 95% sequence identity with ~~the mature TGF- β 1 as presented in residues 279-283 and 296-407 of SEQ ID NO: 37~~ and which retains TGF- β 1 activity;
wherein the functionalizing peptide tag is inserted between a pair of adjacent
residues between about ~~residues-positions~~ 1 and 22 of the mature portion of the TGF- β 1;
and wherein the activity of the TGF- β 1 fusion protein is reduced by no more than 50% as compared to the mature TGF- β 1.
2. (As presented in Examiner's Amendment) A functional TGF- β 1 dimer formed by the association of two of the fusion proteins of claim 1.

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3. **(As presented in Examiner's Amendment)** The dimer of claim 2, wherein the dimer is a homodimer.

4. **(As presented in Examiner's Amendment)** The dimer of claim 2, made by a process comprising:

expressing a nucleic acid molecule in a eukaryotic cell to produce a monomer fusion protein, wherein the nucleic acid molecule comprises:

a sequence encoding the functionalizing peptide tag;

a sequence encoding the mature TGF- β 1; and

a sequence encoding a pro-region (latency associated peptide) of the TGF- β 1, located to provide targeting and/or assembly and/or processing of the fusion protein encoded for by the nucleic acid.

5. **(As presented in Examiner's Amendment)** The dimer of claim 4, wherein the process further comprises:

associating two monomer fusion proteins to form the dimer.

6. **(As presented in Examiner's Amendment)** The dimer of claim 4, wherein the sequence encoding the pro-region is located upstream to both the sequence encoding the functionalizing peptide tag and the sequence encoding the mature TGF- β 1.

7. **(As presented in Examiner's Amendment)** The dimer of claim 4, wherein the process further comprises:

cleaving the pro-region (latency associated peptide) from at least one fusion monomer.

8. **(As presented in Examiner's Amendment)** The dimer of claim 4, wherein the process further comprises:

cleaving the pro-region (latency associated peptide) from both fusion monomers.

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9. **(As presented in Examiner's Amendment)** The fusion protein of claim 1, wherein the functionalizing peptide tag is inserted downstream of residue five of the mature TGF- β 1.

10. **(Cancelled).**

11. **(As presented in Examiner's Amendment)** The fusion protein of claim 1, where the protein comprises the amino acid sequence as in the mature portion of SEQ ID NO: 37.

12. - 17. **(Cancelled)**

18. **(As presented in Examiner's Amendment)** The fusion protein of claim 1, further comprising a pro-region (latency associated peptide) of the TGF- β 1 located to provide targeting and/or assembly and/or processing of the fusion protein.

19. **(As presented in Examiner's Amendment)** The fusion protein of claim 18, wherein the pro-region is located at the N-terminal region of the fusion protein.

20-27. **(Cancelled)**

28. **(As presented in Examiner's Amendment)** The fusion protein of claim 1, wherein the tag is an epitope tag, a purification tag, or an identification tag.

29. **(As presented in Examiner's Amendment)** The fusion protein of claim 1, wherein the tag comprises a FLAG tag, a c-myc tag, a 6x His tag, a HA tag, a Tat tag, a T7 tag, a GFP peptide, or a GST peptide.

30. **(Cancelled)**

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31. **(Currently amended)** An isolated nucleic acid molecule encoding the fusion protein of claim 1, comprising residues 845-1234 of SEQ ID NO: 36.

[Examiner Nichols: The specified residues encompass the mature, tagged portion of SEQ ID NO: 36.]

32. **(As presented in Examiner's Amendment)** The isolated nucleic acid molecule of claim 31, further comprising a sequence encoding a TGF- β pro-region.

33. **(Currently amended)** The isolated nucleic acid molecule of claim 32, comprising residues 845-1234 of SEQ ID NO: 36.

34. **(As presented in Examiner's Amendment)** A recombinant nucleic acid molecule comprising a promoter sequence operably linked to the isolated nucleic acid molecule according to claim 31.

35. **(As presented in Examiner's Amendment)** An isolated transgenic cell comprising a recombinant nucleic acid molecule according to claim 34.

36. **(As presented in Examiner's Amendment)** The transgenic cell of claim 35, wherein the cell is a bacterial cell or an eukaryotic cell.

37. **(As presented in Examiner's Amendment)** The eukaryotic cell of claim 36, wherein the cell is a yeast cell or a mammalian cell.

38-57. **(Cancelled).**

58. **(As presented in Examiner's Amendment)** A TGF- β 1 fusion protein, comprising:

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a N-terminal region consisting of an amino acid sequence of a pro-region (latency associated peptide) of a TGF- β 1,

a functionalizing peptide tag of no more than about 100 amino acids; and

an amino acid sequence consisting of the mature portion of the TGF- β 1;

wherein the functionalizing peptide tag is inserted between a pair of adjacent residues between about residues 1 and 22 of the mature portion of the TGF- β 1;

and wherein the portion of the fusion protein comprising the mature portion of the TGF- β 1 and the functionalized peptide tag has TGF- β 1 activity that is reduced by no more than 50% as compared to the mature TGF- β 1 alone.

59. (New). An isolated nucleic acid molecule encoding the fusion protein of claim 1, comprising residues 835-1197 of SEQ ID NO: 8, SEQ ID NO: 10, residues 835-1197 of SEQ ID NO: 12, SEQ ID NO: 14, residues 845-1222 of SEQ ID NO: 32, residues 849-1226 of SEQ ID NO: 34, or residues 845-1234 of SEQ ID NO: 38.

[Examiner Nichols: All of the sequences in proposed claim 59 encode the same mature TGF β 1 as in SEQ ID NO: 36. Each sequence also encodes a tag of less than 100 amino acids, which tag is located in the first 22 amino acids of the mature TGF β 1.]

60. (New). An isolated nucleic acid molecule encoding the fusion protein of claim 18, comprising SEQ ID NO: 8, 12, 32 or 38.

[Examiner Nichols: The sequences in proposed claim 60 encode the elements described in proposed claim 59 (see above) together with the LAP portion of TGF β 1 fusion proteins. The LAP sequences are identical to the corresponding nucleotides of SEQ ID NO: 36 except for two nucleotides that differ in each of SEQ ID NOs: 34 and 38. Thus, absent their respective tags, SEQ ID NOs: 8, 12, 32 and 38 have >99% identity to SEQ ID NO: 36.]

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61. (New) The fusion protein of claim 1, where the protein comprises the amino acid sequence as in the mature portion of SEQ ID NO: 9, 11, 13, 15, 33 or 39.

[Examiner Nichols: The sequences in proposed claim 61 are the amino acid sequences encoded by the nucleic acids in proposed claim 59; thus, the proposed claim 59 analysis is applicable here as well.]